Cost-effectiveness analysis of Human Papillomavirus (HPV) Vaccination in the Netherlands

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Editorial

Cost-effectiveness analysis of Human Papillomavirus (HPV) Vaccination in the Netherlands: Recent publication reinforces favorable cost-effectiveness despite misleading conclusion

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Two recent publications in *Vaccine* estimated potential favorable cost-effectiveness for HPV vaccination of teenage girls in the Netherlands [1,2]. Just a few months ago, de Kok et al. concluded in another journal that "In the Netherlands, HPV vaccination is not cost-effective even under favorable assumptions" [3]. I highly appreciate their thorough analysis of vaccinating 12-year-old Dutch girls and their elegant model developed, but would argue that this specific conclusion of their paper is based on inadequately selecting the analyses considered to be the most important ones. In particular, the authors present a cost-effectiveness ratio of €53,500 per quality-adjusted life-year (QALY) gained as their primary result, based on a specific set of assumptions and parameters. Notably, discount rates of 3% for both money and QALYs were underlying this cost-per-QALY estimate. To provide insight on the variability around this result, in sensitivity analysis broad ranges for assumptions and parameters were investigated, again using discount rates of 3% over the whole spectrum.

Nowadays, many countries have defined guidelines on the methodology for adequately performing cost-effectiveness analysis [4]. Such guidelines are crucial for achieving consistent and comparable economic analyses for innovative drugs, vaccines and diagnostics that potentially enter the health-care market through the frameworks of reimbursement within national drug systems, vaccination programs and health-insurance plans. In times when limits of health-care budgets seem to increasingly put forward actual constraints on reimbursement, such consistent and comparable analyses are eminent if one wants to validly decide what to reimburse and what to deny. Also, the Netherlands has defined such guidelines for "good health-economic practice", involving areas such as sensitivity analysis, sources for standard costing of health-care resource use, methods for QALY measurement and discounting [5]. The development of these guidelines went along a careful process, involving experts from medical, pharmaceutical, pharmacoeconomic and health-economic sciences and international consultations [5].

The specific guideline for discounting prescribes the application of different discount rates for money and QALYs, in particular at 4% and 1.5%, respectively. (Notably, discounting is preformed to correct for time preference.) These rates were derived from applying a previously validated mathematical economic model for such differential discounting, to the specific Dutch situation [6,7]. With most other countries prescribing similar discount rates for money and QALYs in their guidelines rather than differential discounting, the Dutch rates had to be strongly defended in the scientific literature [8–10]. Some key aspects in this debate referred to the lack of comparability of cost-effectiveness analyses performed using differential discounting with previous analyses and analyses in other countries on the one hand, versus underlying strong arguments of differential growth rates achieved in the overall economy and in the health-care sector justifying differential discounting on the other hand. Obviously, this debate has further strengthened the credibility of differential discounting and Belgium and Luxemburg have now taken over this Dutch discounting guideline [4]. In the Netherlands, all new innovative drugs submitted for reimbursement in recent years for the drugs reimbursement system had to present a cost-effectiveness analysis performed conform the guidelines, inclusive adequate discounting at the rates mentioned. In fact, both HPV-vaccines have gone through this procedure in attempting reimbursement for those groups outside the national vaccination program, notably women of 17 years and older [11]. Analyses on new drugs that fail to apply the adequate discount rates are neglected in the reimbursement decision-making process as they come up with incomparable results and are thus inherently irrelevant.

With discounting at 3% for both money and QALYs, de Kok et al. obviously do not apply the adequate discount rates, rendering – I would argue – their primary analysis as irrelevant. In the latter section of their paper, the authors do state that "... the Dutch Health Care Insurance Board ... recommended that costs and effects were to be discounted at 4% and 1.5%, respectively, per year ... applying these rates would reduce the costs for HPV vaccination ... to €19,700 per QALY gained". Unfortunately, no sensitivity analysis surrounding this value is now presented in the paper, thus lacking to provide crucial insights on the robustness of this specific, yet most important value. So, rather than presenting the €19,700-per-QALY value as their primary result and perform adequate sensitivity analysis surrounding this, de Kok et al. built their analyses and arguments on a cost-per-QALY estimate derived using discount rates at 3% that have never been discussed in the Netherlands, are certainly not in the guideline and actually are irrelevant for the Dutch deci-

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sion context. Strikingly, the authors provide no rationale nor any reference for their choice on discount rates. It is generally known that results on cost-effectiveness of vaccines are highly sensitive to the exact discount percentages chosen [12,13], further strengthening the relevance of using the appropriate rates in this specific case of HPV vaccination.

As the design of the model by de Kok et al. is comparable to that published by other research groups that estimated cost-effectiveness of HPV vaccination [1,2,14], comparable cost-effectiveness ratios from these analyses would be expected. Indeed, if the only relevant ratio from de Kok et al. at €19,700 would be taken, the similarity is striking. All analyses come up with cost-effectiveness ratios varying from €18,000 to just under €20,000 per QALY. Cost-effectiveness ratios below or even just above €20,000 per QALY are certainly generally considered "cost-effective" in the Netherlands and justifying the implementation of the respective medical technology under consideration [15,16]. So, several independent analyses – inclusive the one by de Kok et al. – have now assessed that cost-effectiveness of HPV vaccination of young teenage girls is cost-effective. Lacking in the paper by de Kok et al. paper, yet present in the others, sensitivity analyses proved that this result is quite robust for varying relevant assumptions in the model within plausible ranges. I conclude that the conclusion by de Kok et al. is misleading, should be re-visited and would probably better be formulated as "In the Netherlands, HPV vaccination is likely to be cost-effective if compared with screening alone", and that is fully in line what other studies – with 2 of them in *Vaccine* – recently found [1,2,14].

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